DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-399

AstraZeneca Pharmaceuticals LP
Attention: Ronald Falcone, Ph.D.
Regulatory Affairs Director
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Dr. Falcone:

Please refer to your new drug application (NDA) dated August 2, 2002, received August 5, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for IRESSA™ (gefitinib tablets).

We acknowledge receipt of your submissions dated July 30, November 2, 5, 9 and 30, and December 27, 2001; January 31; March 18 (2) and 21; April 3 and 4; May 3, 7 and 23; July 3, 10, 15, 22, 23 and 26; August 2 (2), 16 and 20; September 26; October 17, 21, 22 and 31; November 15 and 27; December 12 and 24, 2002; and January 3, 8, 17, 21, 24 and 27; February 6, 19 and 25; March 14; April 3 and 11, 2003.

This new drug application provides for the use of IRESSA™ (gefitinib tablets) as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of both platinum-based and docetaxel chemotherapies.

We completed our review of this application, as amended, according to the regulations for accelerated approval. It is approved, effective on the date of this letter, for use as recommended in the enclosed labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and immediate container label). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-399.**" Approval of this submission by FDA is not required before the labeling is used.

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. We remind you of your post marketing study commitments specified in your submission dated May 1, 2003. These commitments, along with any completion dates agreed upon, are listed below.

1. To conduct, submit, and publish the final study report for Protocol 1839IL/0709 entitled "A randomized phase III survival study comparing ZD1839 (Iressa ™) plus best supportive care (BSC) versus placebo plus BSC in subjects with advanced NSCLC who have received one or two prior regimens and are refractory or intolerant to their most recent regimen." Survival is the primary study endpoint. We refer you to our letter of April 1, 2003 detailing the Division response to your Special Protocol Assessment request. Further, as stated in your letter of February 19, 2003 the first patient should be enrolled in this study in early July 2003. Enrollment should be completed by April 2005, and study results should be submitted to the Division in October 2005.

2. To conduct, submit, and publish the final study report for a randomized trial comparing gefitinib and taxotere in NSCLC. The primary endpoints should be survival and time to progression. A secondary endpoint should evaluate cancer-related symptoms. The study should enroll at least 800 patients. A detailed protocol should be submitted to the Division as an SPA by June 13, 2003, with the first patient enrollment by November 2003 and the study report submitted to the Division by December 2006.

3. To conduct, submit, and publish the final study report for a randomized, controlled, double-blind, study comparing ZD1839 treatment with best supportive care in refractory, symptomatic, stage III/IV NSCLC patients (PS 0-2, LCS $\leq$ 20). Symptom improvement should be the primary endpoint of this study. A detailed protocol should be submitted to the Division as an SPA by June 13, 2003, with the first patient enrollment by November 2003 and the study report submitted to the Division by June 2005.

Submit final study reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to these postmarketing study commitments must be clearly designated "Subpart H Postmarketing Study Commitments."

In addition, we note your following postmarketing study commitments, specified in your submission dated May 1, 2003, that are not a condition of the accelerated approval. These commitments are listed below:

1. To submit a final study report of BR19 (NCIC, EORTC), a Phase 3 prospective randomized, double-blind, placebo-controlled trial of the epidermal growth factor receptor antagonist, ZD 1839 in 1,160 patients with completely resected primary Stage 1, 2, and 3A non-small cell lung cancer. The study will have 90% power to detect a 33% increase in median survival. Secondary endpoints include disease-free survival, safety, and EGFR expression. The study opened in October 2002. The accrual rate is projected to be 390 patients per year for 3 years. A 2-year follow-up is planned. A study report is to be submitted to the Division by the first quarter of 2008.

2. **SWOG 0023** Randomized, multicenter, double blind placebo-controlled trial of cisplatin/etoposide/ radiotherapy with consolidation docetaxel followed by maintenance therapy with ZD 1839 or placebo in patients with inoperable advanced Stage III non-small cell lung cancer. Eight hundred-forty patients will be enrolled with approximately 670 patients eligible for the randomization between ZD1839 and placebo. The primary endpoint is survival. The study will have 90% power to detect a 33% increase in median survival. The study has been open for 1 year. Projected accrual time is 3.5 years. A minimum follow-up of 30 months is planned. The study report is to be submitted to the Division by the fourth quarter 2008.

3. To submit reports of all medication errors, both potential and actual, that occur within the United States with IRESSA for two years following the date of approval. Potential errors should be reported and summarized quarterly. All actual errors should be submitted within 15 days regardless of patient outcome. Yearly reports of potential and actual errors occurring with IRESSA should be submitted for two years following the date of approval. Within one month of approval, AstraZeneca Pharmaceuticals will meet with FDA to clarify the meaning of the terms potential medication error and actual medication error.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled **"Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."**

As required by 21 CFR 314.550, submit all promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement. Send two copies of all promotional materials directly to:

Division of Drug Marketing, Advertising
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville MD 20857

In addition, as required by 21 CFR 314.550, submit all subsequent promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement. Send two copies of the promotional materials and the package insert to the address above.

FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Amy Baird, Regulatory Project Manager, at (301) 594-5779.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure